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DINSMORE & SHOHL, LLP
1900 CHEMED CENTER
255 EAST FIFTH STREET
CINCINNATI, OH 45202

EXAMINER
CHUNDURU, SURYAPRABHA

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 18

Application Number: 09/743,023
Filing Date: March 07, 2001
Appellant(s): HEMMENDORFF ET AL.

Clare M. Iery
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 1, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-3, 5-8, 11-13 15-22 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,663,304	Builder et al.	9-1997

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-3, 5-8, 11-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Builder et al. (USPN. 5,663,304).

Builder et al. teach a method for production of recombinant peptides comprising fermenting cells (host cells) to produce recombinant peptides in the presence of metal salt (alkali metal salt) prior to peptide isolation (see column 26, lines 34-67, column 27, 1-67, column 28, lines 15-33, column 6, lines 42-67, and column 7, lines 1-9). Builder also teach that (i) the use of metals facilitate disulfide oxidation of polypeptides and yield correct refolding of a misfolded polypeptide contained in host cells (see column 6, lines 42-60); metal salts include sodium chloride, potassium chloride, sodium phosphate, potassium phosphate (see column 28, lines 15-

33, column 11, lines 42-54); alkali metal salt buffer (pH 10.5) was added after fermentation and pH was adjusted to 3.5 with phosphoric acid (see column 28, lines 28-33 and column 16, lines 47-55); recombinant polypeptides of interest include human growth factor (see column 8, lines 24-67, and column 9, lines 1-10). Thus, the disclosure of Builder et al. meets the limitations in the instant claims.

(11) Response to Argument

The instant invention as well as the method of Builder et al. are directed to a method for the production of recombinant peptides.

Introduction to the subject matter

The production of a biologically active recombinant protein depends on the folding and assembly of these proteins into their native three-dimensional structures so that they may function correctly. There are three major parameters that are required to achieve successful protein folding and assembly in vitro. They are (i) temperature, (ii) protein concentration, and solvent conditions. Optimally, refolding is performed at a low temperature to reduce the influence of hydrophobic interactions. Low protein concentration is not favorable because it leads to misfolding and aggregation. Appropriate solvent conditions are required to maximize correct folding and minimize misfolding and aggregation. Neutral pH and several refolding buffer additives aid in mimicking some qualities of the in vivo solvent environment of the cytoplasm. The instant invention and the method of Builder et al. are targeted to the method for production of correctly folded recombinant proteins or peptides.

Appellants argue that the claims 1-3, 5-8 and 11-22 are not anticipated by and patentably distinguishable from Builder et al. This argument is not be considered persuasive for the following reasons:

Appellants argue on page 6 of the Appeal brief, that there is no teaching or reference for reducing trisulfide formation in the production of recombinant peptides in the disclosure of Builder et. al. This argument is not persuasive because the claimed method and that of Builder et al. result in the production of correctly folded recombinant polypeptides or proteins. As MPEP 2112 states, "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Because both methods (that of the claimed invention and of Builder et al.) yield the same result (i. e. properly folded recombinant polypeptide), the reduction of trisulfides is inherent. Further Builder et al. disclose the addition of metal salt to the solvent medium explicitly to improve correct folding of the recombinant polypeptides, through out the patent for example:

(i) on column 6 of the patent ('304), Builder et al. disclose pH 7-12 and addition of alkali metal to increase the production of correct folding of a misfolded recombinant polypeptide (see lines 52-60);

(ii) on column 7, of the patent ('304), Builder et al. disclose the importance of adding metal salts to enhance refolding of misfolded polypeptides and avoiding the use of expensive disulfide exchange agents such as glutathione (see lines 10-28);

(iii) on column 11, of the patent ('304), Builder et al. disclose alkaline earth, alkali metal, or ammonium salt include sodium chloride, ammonium chloride, potassium citrate, magnesium chloride, calcium phosphate etc. (see lines 42-54);

(iv) on column 12, of the patent ('304), Builder et al. disclose a key ingredient of the buffer used in the process of producing recombinant polypeptide, is an alkaline earth, alikali metal, or ammonium salt and effective amount of alkali metal salt (see lines 12-54).

(v) on columns 15-16, of the patent ('304), Builder et al. disclose different culture media, which basically comprise metal salts (see column 15, lines 52-67, column 16, lines 1-12)

Builder et al. disclose the addition of metal salts which would inherently reduce the formation of trisulfides, the inherency naturally flows from the discosure of Builder et al. because for correct folding disulfide bonds (S-S bonds) and inhibition of intermediate aggregates of misfolded proteins is favored. Builder et al. disclose the role of metal salts in producing correctly folded polypeptides, wherein Builder et al. disclose the importance of adding metal salts in reducing protein aggregates or misfolded polypepetide aggregation (see column 7, lines 10-28). The method as disclosed by Builder et al. inherently teaches a reduction in the amounts of trisulfides because in the process of refolding of recombinant protein, free sulfhydryl groups and disulfides are formed constantly, and to enhance the solubility of these intermediate conformations of protein, a suitable buffer is suggested by Builder et al. (see column 3, lines 1-8). Further, to achieve correct folding, weakly denaturing solution is provided and desulfonating the protein was performed to ensure suitable disulfide bonds remain intact (see column 3, lines 9-22). Therefore, the prior art of the record inherently teaches low trisulfides and meets each of the limitations found in the claims. Further, the claim is of the open "comprising" format, which

permits the inclusion of additional elements, so that any additional steps are permitted in the claim.

Appellants' arguments on page 7 of the Appeal brief, that the preamble of the claim should be given patentable weight, is persuasive for the following reasons. First, As MPEP 2111.02 states, "If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction." In the instant invention the limitation "low amounts of trisulfides" in the preamble of the present claims does not provide any significance to the claim construction because the claims are directed to the production of recombinant polypeptides, but not to the low amounts of trisulfides or formation of reduced trisulfides. Second, even if it is given patentable weight, Builder et al. inherently teaches this limitation by adding metal salt to the process as discussed above.

Appellants also argue that the actual values or concentration of the limitation "low amounts of trisulfides" is not applicable to the instant claims 2 and 13-22, which clearly show that applicants agree that the recitation of actual values or concentrations are required for claims 1,3, 5-8, 11-12. If the preamble should be given patentable weight, it should be recognized that the instant claims are more inclined to production the low trisulfides or reduction of the amount of trisulfides, wherein the process steps do not recite how this limitation is achieved except for recitation of adding metal salts to the fermenting medium or after fermentation, which is recognized explicitly by Builder et al. (see column 6, lines 52-60, column 7, lines 10-28, column 12, lines 12-54).

Appellants' arguments on page 8 of the appeal brief, regarding the mechanism of formation of trisulfides and production of trisulfide are not on point because the limitation in the preamble of the present claims is at issue. Appellants also argue that Builder et al. disclose the production of Insulin-like growth factor (IGF-I) which is not known to produce trisulfides. This argument is not persuasive because Builder et al disclose that the process can be used not only to produce IGF-I but also to produce preferred mammalian recombinant polypeptides such as growth hormone, IGF-II, brain IGF-I, relaxin chains, neurotropins (see column 9, lines 10-20). The issue here is the production of recombinant polypeptides using metal salts.

Further Appellants argue that the instant claims 5 and 15 recite the limitation "pH is equal to or lower than pH 7, which is not persuasive because Builder et al. explicitly teach such pH conditions throughout the patent, for example,

(i) on column 16, of the patent ('304), Builder et al. disclose the pH range as 5 to 9, more preferably 6 to 8 which indicate the pH limitation lower or equal to pH 7 (see lines 47-55);

(ii) on column 28, of the patent ('304), Builder et al. disclose the pH of the medium adjusted to 3.5, after fermentation step (see lines 15-33);

(iii) on column 31, of the patent ('304), Builder et al. disclose pH of the medium as 3.0, after fermentation (see lines 54-63).

Thus, the arguments with regards to the limitation pH equal to or lower than 7.0 are not found to be persuasive given the teachings of because Builder et al.

Appellants also argue that there is no teaching or reference to the production of human growth hormone comprising the method as claimed is found not persuasive because as discussed above Builder et al. disclose that the method is used to produce mammalian recombinant

polypeptides such as growth hormone (see column 9, lines 10-20). Thus the method of builder et al. disclose the production of human growth hormone.

Conclusion

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Suryaprabha Chunduru
Examiner
Art Unit 1637

June 6, 2003

Conferees

Gary Benzion, SPE
AU 1637

Remy Yucel, SPE
AU 1636

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

JEFFREY FREDMAN
PRIMARY EXAMINER

Fredman Jeffrey
Primary Examiner
AU 1634

DINSMORE & SHOHL, LLP
1900 CHEMED CENTER
255 EAST FIFTH STREET
CINCINNATI, OH 45202